22 September 2011
EMA/850371/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alimta

pemetrexed

Procedure No.: EMEA/H/C/000564/II/0033

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Invented name/name:	Alimta
International non-proprietary name/common name:	pemetrexed

Indication summary (as last approved):	treatment of malignant pleural mesothelioma and non-small cell lung cancer
Marketing authorisation holder:	Eli Lilly Nederland B.V.

1. Scope of the variation and changes to the dossier

Scope of the variation:	Extension of the existing indication in the maintenance treatment of Non Small-Cell Lung Cancer (NSCLC) other than squamous cell histology after first line chemotherapy. Pemetrexed can be given as maintenance therapy after first line platinum-based chemotherapy including a pemetrexed/platinum combination. Sections 4.1, 4.8 and 5.1 of the SmPC were updated. The Package Leaflet was updated accordingly and minor editorial changes were made to the SmPC, Annex II and PL.
Rapporteur: Co-Rapporteur:	Pierre Demolis Harald Enzmann
Product presentations affected:	See Annex A to the Opinion
Dossier modules/sections affected:	1, 2 and 5
Product Information affected:	Summary of Product Characteristics, Annex II and Package Leaflet (Attachment 1 - changes highlighted)

2. Steps taken for the assessment

Step	Step date
Submission date:	8 February 2011
Start of procedure:	20 February 2011
Rapporteur's assessment report circulated on:	21 April 2011
Co-Rapporteur's assessment report circulated on:	15 April 2011
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 May 2011
MAH's responses submitted to the CHMP on:	21 July 2011
Rapporteur's and Co-Rapporteur's joint	2 September 2011

Step	Step date
preliminary assessment report on the MAH's responses circulated on:	
CHMP opinion:	22 September 2011

3. Scientific discussion

3.1. Introduction

Alimta (pemetrexed) is an antifolate that exerts its antineoplastic activity by disrupting the folate-dependent metabolic processes essential for cell replication. *In vitro* studies have shown that pemetrexed behaves as a multitargeted antifolate by inhibiting thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) which are crucial for the *de novo* biosynthesis of thymidine and purine nucleotides. Polyglutamated metabolites of pemetrexed with prolonged intracellular half-life result in prolonged pemetrexed drug action in malignant cells.

Alimta was granted a Marketing Authorisation (MA) in the European Union (EU) on 20 September 2004. Alimta is indicated:

- in combination with cisplatin for the treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma;

- in combination with cisplatin for the first line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology;

- as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinum-based chemotherapy. First line treatment should be a platinum doublet with gemcitabine, paclitaxel or docetaxel;

- as monotherapy for the second line treatment of patients with locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology.

With this variation application the Marketing Authorisation Holder (MAH) of Alimta proposed to extend the NSCLC maintenance therapy indication to all patients that have received first-line platinum-based chemotherapy, independently of the type of agent the platinum is combined with. In other words, patients need not have received as first line treament a platinum doublet with gemcitabine, paclitaxel or docetaxel, but any platinum-containing combination. For this new indication, the proposed posology is similar to the one authorised for pemetrexed as a single agent: pemetrexed 500 mg/m^2 of body surface area (BSA) administered as an intravenous infusion over 10 minutes on the first day of each 21-day cycle. The MAH proposed to update sections 4.1, 4.8 and 5.1 of the SmPC.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/345/2010) for the following conditions:

- Treatment of lung carcinoma (small cell and non-small cell carcinoma)

On the granting of a class waiver

3.2. Clinical aspects

3.2.1. Introduction

Lung cancer is among the most frequent types of cancer among European men and women and is one of the few that continues to show an increasing incidence. Prognosis is poor with relative 1-year survival rates of approximately 30% and 5-year survival rates around 10%. Although the standardised mortality ratio is declining slightly in men it is still rising in women in the vast majority of European countries.

Lung cancer is subdivided in two groups, the small cell lung cancer (SCLC) and the non small cell lung cancer (NSCLC). SCLC is recognized by its chemo- and radiosensitivity. NSCLC is a heterogeneous group of tumours with common treatment and prognosis. NSCLC accounts for the vast majority of lung cancers (80%, D'Addario et al, 2010*).* NSCLC includes squamous cell carcinoma (40% of cases), adenocarcinoma (35% of cases) and large cell (undifferentiated) carcinoma (25% of cases).

Surgery is the preferred treatment of patients with early disease. However, more than 60-65% of patients present with locally advanced (stage IIIB) or metastatic disease (stage IV) and are not suitable for surgery. Patients with inoperable NSCLC are typically candidates for chemotherapy (D'Addario *et al.* 2005; Azzoli *et a*l. 2009; D'Addario *et al.* 2010; NCCN 2011). For patients with a disease staged as IIIB or IV the primary goal of therapy is palliative. Moderate gains in survival and other outcomes like time to disease progression and quality of life have been shown with platinum-based chemotherapy. Despite recent advances in treatment, the prognosis for patients with locally advanced or metastatic NSCLC remains poor. Only one third of patients obtain an objective response with initial chemotherapy, with an overall survival time of 7 to 13 months (Pfister *et al*. 2004; Wakelee and Belani 2005; Sandler *et al.* 2006; Scagliotti *et al.* 2008; Manegold *et al.* 2008; Levy *et al.* 2010).

Platinum-based combination regimens with gemcitabine, vinorelbine, or taxanes (paclitaxel or docetaxel) have been the mainstay for the initial treatment of locally advanced or metastatic NSCLC (Pfister *et al*. 2004; NCCN 2011). Platinum-based doublets are preferred over non-platinum combinations (Azzoli *et al*. 2009).

The addition of bevacizumab to standard doublets has been shown to improve upon the standard chemotherapy regimens (Sandler *et al*. 2006). The most recent ASCO, ESMO, and NCCN guidelines have been updated to add pemetrexed and irinotecan to the list of third generation cytotoxics, as well as the addition of bevacizumab to platinum-based therapy (Azzoli *et al*. 2009; D'Addario *et al.* 2010; NCCN 2011).

Alimta (pemetrexed) was initially authorised in the EU in the indications (combination treatment of) mesothelioma and second line NSCLC (as monotherapy). The second line monotherapy NSCLC indication, granted based on the results of the JMEI pivotal trial, was then both extended and restricted by two variations of the marketing authorisation.

With variation EMEA/H/C/000564/II/09 (EC Decision date: 8 April 2008) and based on the results of the JMDB pivotal trial, a first-line NSCLC indication (in combination with cisplatin) was approved. At the same time, it had become more and more obvious that pemetrexed is active only in non-squamous NSCLC histologies. As a result, the first line indication was limited to non-squamous histologies and the originally granted second line was restricted accordingly.

A NSCLC maintenance indication after first-line chemotherapy was approved in 2009 (variation EMEA/H/C/00054/II/15, EC Decision date: 02 July 2009) based on the results of one pivotal, multicenter, randomised, double-blind, placebo controlled phase III study (JMEN), which compared the efficacy and safety of maintenance treatment with pemetrexed plus BSC with that of placebo plus BSC

in 663 patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC who had not progressed after 4 cycles of first line doublet therapy containing cisplatin or carboplatin in combination with gemcitabine, paclitaxel, or docetaxel.

Another agent approved for maintenance treatment of NSCLC patients with stable disease after first-line platinum-based doublet chemotherapy is erlotinib. However, no studies have examined the benefit of maintenance therapy immediately following treatment with a pemetrexed-platinum induction regimen. Pemetrexed-containing regimens were not included in previous advanced NSCLC maintenance studies, including Study JMEN (pemetrexed), SATURN (erlotinib), and ATLAS (erlotinib and bevacizumab combination) (Ciuleanu *et al.* 2009; Cappuzzo *et al.* 2010; Miller *et al*. 2009). This question was addressed with the pivotal trial of this variation application, the PARAMOUNT Study described in detail below.

GCP

The MAH has provided a statement that the PARAMOUNT study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices (GCPs) and the applicable laws and regulations.

3.2.2. Clinical Efficacy

The main study supporting this application was the PARAMOUNT (H3E-EW-S124) study.

PARAMOUNT (H3E-EW-S124)

This was a randomised, double-blind, placebo-controlled Phase III study, comparing the efficacy and safety of maintenance pemetrexed plus best supportive care (BSC) with that of placebo plus BSC in patients with a diagnosis of Stage IIIB/IV NSCLC who had not progressed after 4 cycles of induction therapy with pemetrexed and cisplatin.

Methods

Study Participants

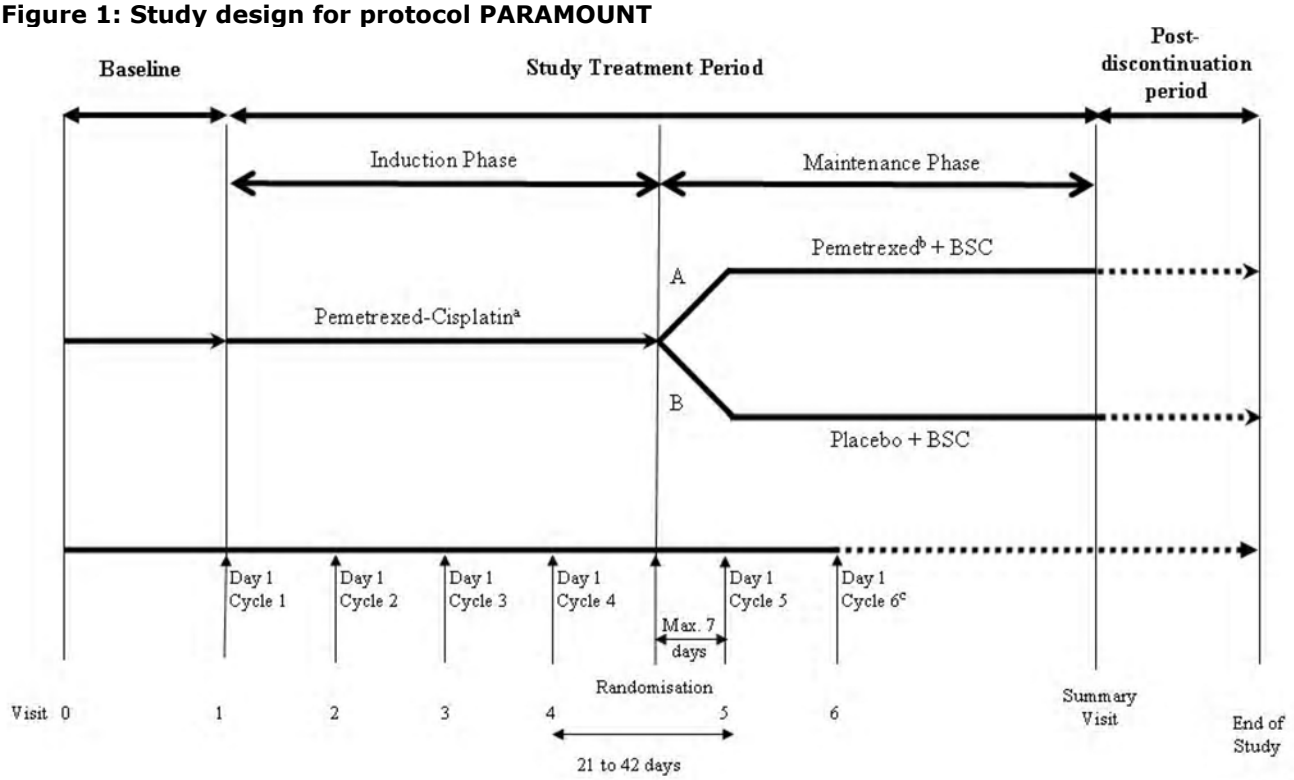
The main inclusion and exclusion criteria were the following:

Inclusion criteria	Exclusion criteria
Induction Phase	
- Histological or cytological diagnosis of NSCLC defined as other than predominantly squamous cell histology (squamous cell and/or mixed small cell, non-small cell histology is not permitted) - Stage IIIB or Stage IV prior to induction therapy that is not amenable to curative therapy - ECOG PS of 0 or 1 - No prior systemic chemotherapy for lung cancer - Patients with prior radiation therapy may be eligible - At least 1 unidimensionally measurable lesion meeting RECIST - Estimated life expectancy of at least 12 weeks	- Patients who received treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry - Patients previously completed or withdrawn from this study or any other study investigating pemetrexed - Serious concomitant systemic disorder - Serious cardiac condition - Prior malignancy other than NSCLC, carcinoma in situ of the cervix, or non-melanoma skin cancer, unless that prior malignancy was diagnosed and definitively treated at least 5 years previously with no subsequent evidence of recurrence
Maintenance Phase	
- ECOG PS of 0 or 1 - Documented radiographic evidence of a tumour response of CR, PR, or SD	- Exclusion Criteria for the Induction Phase

Treatments

The study had 4 periods: a baseline period, an unblinded induction treatment period, a blinded maintenance treatment period and a post-discontinuation period (see also Figure 1 below).

Figure 1: Study design for protocol PARAMOUNT



a Pemetrexed (500 mg/m2, Day 1) plus cisplatin (75 mg/m2, Day 1). b Pemetrexed (500 mg/m2, Day 1). Patients who required a dose reduction of pemetrexed during induction treatment, and who were eligible to receive maintenance treatment, started blinded maintenance treatment (pemetrexed or placebo) at the reduced dose.
c Subsequent cycles during the maintenance phase followed the same guidelines as Cycle 6. Patients were allowed to continue to receive study therapy until 1 of the reasons for discontinuation of study drug was met.

All patients were treated during **induction** with AC (pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 on Day 1 of a 21 day-cycle, completion of four cycles was required per protocol).

Patients with a documented Complete Response (CR), Partial Response (PR), or Stable Disease (SD) after completion of induction chemotherapy and an ECOG (Eastern Cooperative Oncology Group) performance status (PS) of 0 or 1 were randomly assigned to receive as **maintenance:**

Experimental Arm A: pemetrexed 500 mg/m^2 on Day 1 every 21 days + BSC

Control Arm B: placebo on Day 1 every 21 days + BSC

All patients enrolled into this study received pemetrexed and were required to take folic acid, vitamin B12, and dexamethasone (as described in the SmPC of Alimta). All randomised patients were required to take vitamin supplementation and dexamethasone during the maintenance phase of the treatment period to maintain the double-blind design of the study. Maintenance therapy continued until the patient met 1 or more of the specified reasons for discontinuation, including Progressive Disease (PD).

Objectives

The objective of this trial was to compare maintenance therapy with pemetrexed plus BSC versus placebo plus BSC in patients with stage IIIB (with pleural effusion and/or positive supraclavicular lymph nodes) or stage IV non-squamous NSCLC whose disease had not progressed during 4 cycles of pemetrexed and cisplatin induction chemotherapy.

Outcomes/endpoints

Objective Progression Free Survival (PFS) was the primary efficacy variable in this study. Objective PFS time was defined as the time from the date of randomisation to the first date of objectively determined PD or death from any cause. For patients not known to have died as of the data cut-off date and who did not have objective PD, PFS was censored at the date of the last objective progression-free disease assessment.

Investigator assessments of radiological data were considered primary for the analyses of PFS [and objective tumour Response Rate (RR)]. An independent review of radiological data (lesion measurements based on CT scans) was conducted and any revisions of measurements resulting from the review were used for sensitivity analyses.

Secondary endpoints included: Overall Survival (OS), objective tumour Response Rate (RR) assessed using RECIST (Response Evaluation Criteria In Solid Tumors), patient-reported outcomes using the EQ-5D questionnaire and toxicity [AEs rated using the National Cancer Institute (NCI) CTCAE (Common Terminology Critertia for Adverse Events) scale].

Overall survival (OS) time was defined as the time from the date of randomisation to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS was censored at the last contact date (last contact for patients in post-discontinuation period = last known alive date in mortality status).

The EQ-5D (EuroQol Group 1990) is a standardised, non-disease-specific instrument for describing and valuing health status that has been used previously with cancer patients (Pickard et al. 2007). The EQ-5D is a self-administered health-status questionnaire consisting of 2 parts.

- The first part includes 5 descriptive questions relating to mobility, self care, usual activities, pain/discomfort, and anxiety/depression, on which the patient is required to rate his/her health. Each attribute has 3 levels: no problem, some problems, and major problems, thus defining 243 possible health states, to which has been added "unconscious" and "dead" for 245 in all.

- The second part of the EQ-5D is a Visual Analogue Scale (VAS) that allows patients to rate their present health condition. Possible scores range from 0 (worst imaginable health state) to 100 (best imaginable health state).

The 245 health states defined by the 5-dimensional descriptive system can be converted into a weighted health-state index by applying a method described in detail by Dolan (1997). This method permits the measurement of preferences. The possible values for health utility ranges from -0.59 (severe problems in all 5 dimensions) to 1.0 (no problem in any dimension) on a scale where 0 represents death and 1 represents the best possible health state (Shaw et al. 2005). The EQ-5D has been translated and validated into 102 official languages, including French, German, and Spanish. The EQ-5D was completed by only those patients for whom a translation is available in his/her native language. Patients were expected to complete the questionnaire at the following times:

- at baseline, after consent
- on Day 1 of each cycle of induction therapy (The Cycle 1 Day 1 assessment does not have to be completed if the baseline assessment is completed within 7 days prior to Day 1 of Cycle 1)
- on Day 1 of each cycle of maintenance therapy
- at the 30-day post-discontinuation visit - assessments were completed prior to treatment administration on days that the patient received therapy.

Sample size

The sample size of 558 randomised patients was derived assuming the true OS hazard ratio (HR) was 0.70 and assuming 390 events (30% censoring) in the final analysis of OS. This sample size was selected for this study to provide 93% statistical power for the final analysis of OS. Under the assumption that the true PFS hazard ratio (HR) was 0.65, the primary unadjusted log-rank test of PFS had 90% power to show a statistically significant difference between arms provided that there were at least 238 events included in the analysis. Therefore, the primary analysis of PFS was to occur after at least 238 events (57% censoring) of progressive disease or death were confirmed among randomised patients.

Randomisation

Patients were randomised in a 2:1 ratio, allocating twice as many patients to the pemetrexed plus BSC arm. Randomisation was stratified for the following 3 prognostic factors after completion of the first 4 cycles of induction chemotherapy with pemetrexed and cisplatin: ECOG PS just prior to randomisation (0 versus 1), tumour response to induction chemotherapy (CR/PR versus SD) and disease stage prior to administration of induction therapy (IIIB versus IV).

Blinding (masking)

This was a double-blind study.

Statistical methods

Baseline and efficacy analyses used the ITT population which included all patients who were randomised (analysed by treatment arm as randomised).

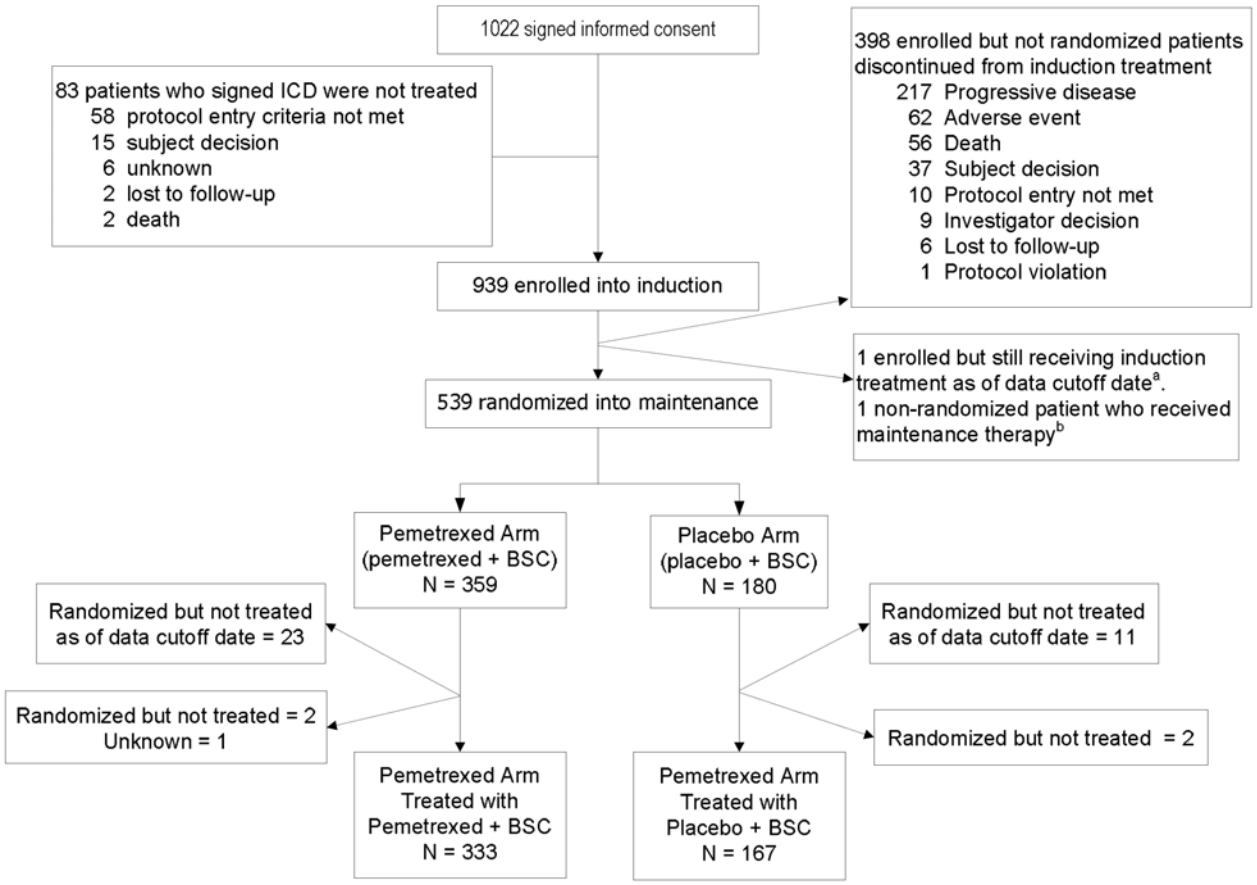
All patients enrolled in the study (treated with at least 1 dose of pemetrexed or cisplatin during the induction phase) were evaluated for safety.

The type 1 (alpha) error was controlled for the analyses of both PFS and OS, in order to maintain an overall 2-sided alpha level of 0.05, using the following statistical gate-keeping and alpha-spending scheme:

- The primary statistical test of PFS was performed using a nominal 2-sided alpha level of 0.05.
- A 2-sided nominal alpha level of 0.05 was divided between two preliminary and one final analysis of OS: a nominal 2-sided level of 0.0001 was spent for each preliminary analysis of OS, leaving a nominal level of 0.0498 to be spent for the final analysis of OS. If the primary test of PFS was statistically significant, then by application of statistical gate-keeping the overall 2-sided alpha level was maintained at 0.05.

Results

Participant flow



Recruitment

The first patient was enrolled on 19 November 2008 and the last patient was enrolled on 23 April 2010. At the clinical cut-off date (30 June 2010) 179 patients (pemetrexed: 136, placebo: 43) were still receiving maintenance treatment.

Conduct of the study

There were 2 amendments to the study protocol. The original trial sample size (570 patients treated in induction, 399 patients randomised to maintenance treatment) was selected based on a power calculation for the analysis of PFS, assuming a HR of 0.70 and 25% censoring.

The protocol was amended on 06 October 2008 to include a power calculation for the analysis of OS. The new sample size determined that 600 patients treated in induction were needed to provide 372 patients randomised to maintenance treatment. The calculation assumed a PFS HR of 0.65 and 36% censoring for PFS, and an OS HR of 0.70 and 30% censoring for OS. The trial would be fully powered for PFS (90%) and OS (80%).

The protocol was amended on 20 July 2009 to increase the power of the OS analysis by increasing the number of patients entering the induction and maintenance treatment periods. The new sample size determined that 900 patients treated in induction were needed to provide 558 patients randomised to maintenance treatment. The calculation assumed a PFS HR of 0.65 and 52% censoring for PFS, and an OS HR of 0.70 and 30% censoring for OS.

The increase in survival to at least 390 events increased the power of the analysis from 80% to 93%; for PFS, 90% power was maintained, provided that at least 238 events were included in the analysis. The final a priori SAP (version 2) was finalised and approved (30 June 2010) prior to data lock and unblinding of the aggregate database for the final PFS analysis.

A total of 96 randomised patients (17.8%) were reported to have at least 1 protocol violation. The only identified protocol violations for the randomised patient population were for the incorrect dose modification category (9.5%) and the protocol inclusion/exclusion criteria category (8.5%). Protocol inclusion/exclusion criteria violations included continuing study treatment after PD (4.1%), randomisation even though response to induction treatment was not CR, PR, or SD (3.2%), randomisation with <4 cycles of induction treatment (1.5%), and randomisation even though PS was not 0 or 1 following induction treatment (0.6%). In general, protocol violations in this study were balanced between study arms.

Baseline data

The study arms were balanced with respect to demographic characteristics (see Table 1 below). Among all patients randomised, the median age was 61.4 years, and the majority of patients were Caucasian (94.6 %), male (58.1 %), and reported a history of smoking (77.7%). The two treatment arms were also balanced in terms of stratification factors (Table 2), histological type of NSCLC (Table 3) and concomitant medications received on study (data not shown).

Table 1: Patient Demographic Characteristics at Baseline, All Randomised Patients, Baseline Characteristics (Prior to Randomisation)

	Variable	Pemetrexed N = 359	Placebo N = 180	Total N = 539
Gender n (%)	Male Female	201 (56.0) 158 (44.0)	112 (62.2) 68 (37.8)	313 (58.1) 226 (41.9)
Age at randomization (years)	Median age Minimum Maximum	60.95 31.92 78.67	62.35 34.94 83.28	61.39 31.92 83.28
Age group n (%)	Age <65 years Age >65 years	238 (66.3) 121 (33.7)	112 (62.2) 68 (37.8)	350 (64.9) 189 (35.1)
Origin n (%)	Asian African Caucasian	16 (4.5) 4 (1.1) 339 (94.4)	8 (4.4) 1 (0.6) 171 (95.0)	24 (4.5) 5 (0.9) 510 (94.6)
Smoking status n (%)	Ever smoker Never smoker Unknown	275 (76.6) 82 (22.8) 2 (0.6)	144 (80.0) 34 (18.9) 2 (1.1)	419 (77.7) 116 (21.5) 4 (0.7)

Abbreviations: N = number of randomized patients; n = number of patients in category.

Table 2: Baseline Randomization Factors by Study Arm, All Randomised Patients, Baseline Characteristics (Prior to Randomisation)

	Variable	Pemetrexed N = 359	Placebo N = 180	Total N = 539
ECOG PS at randomization, n (%)	0	115 (32.0)	55 (30.6)	170 (31.5)
	1	243 (67.7)	123 (68.3)	366 (67.9)
	2[a]	0 (0.0)	1 (0.6)	1 (0.2)
	3[a]	1 (0.3)	1 (0.6)	2 (0.4)
Disease stage prior to induction therapy, n (%)[b]	Stage IIIB Stage IV	31 (8.6) 328 (91.4)	19 (10.6) 161 (89.4)	50 (9.3) 489 (90.7)
Best tumour response to induction therapy, n (%)	Complete/Partial Response	166 (46.2)	76 (42.2)	242 (44.9)
	Stable Disease	186 (51.8)	94 (52.2)	280 (51.9)
	Progressive Disease[a]	1 (0.3)	3 (1.7)	4 (0.7)
	Unknown [a]	6 (1.7)	7 (3.9)	13 (2.4)

Abbreviations:N = number of randomised patients; n = number of patients in category. a Randomized patients with an ECOG PS of 2 or 3, or a best response to induction therapy of progressive disease or unknown were considered protocol violations. b Lung Cancer Staging Guidelines Version 5 (Fleming et al. 1997).

Table 3: Histologic Classifications by Study Arm, All Randomised Patients, Baseline Characteristics (Prior to Induction)

Histologic Classifications [a, b]	Lilly Assigned System Codes	Pemetrexed N = 359	Placebo N = 180	Total N = 539
Adenocarcinoma		**310 (86.4)**	**161 (89.4)**	**471 (87.4)**
Bronchoalveolar carcinoma	2140	6 (1.7)	2 (1.1)	8 (1.5)
Adenocarcinoma	1882	304 (84.7)	158 (87.8)	462 (85.7)
Other[c]	100	0	1 (0.6)	1 (0.2)
Large-Cell Carcinoma	920	**24 (6.7)**	**12 (6.7)**	**36 (6.7)**
Otherd or Indeterminate		**25 (7.0)**	**7 (3.9)**	**32 (5.9)**
NSCLC NOS	1897	14 (3.9)	2 (1.1)	16 (3.0)
Poorly differentiated NSCLC	1432	11 (3.1)	5 (2.8)	16 (3.0)

Abbreviations: N= number of randomized patients; NSCLC= non-small cell lung cancer; NOS= not otherwise specified; a Grouped by WHO classification of lung tumours (Travis et al. 1999) b Patients with squamous-cell carcinoma were not eligible to enroll. c Adenocarcinoma, Mucinous d The subcategory of "other" represents patients with a primary diagnosis of NSCLC whose disease did not clearly qualify as adenocarcinoma or large-cell carcinoma.

Numbers analysed

539 patients were randomly assigned (2:1) to receive pemetrexed plus BSC (359 patients) or placebo plus BSC (180 patients) during maintenance treatment. Of the randomised patients, 333 (92.8%) on the pemetrexed arm and 167 (92.8%) on the placebo arm received at least 1cycle of maintenance treatment as of the data cut-off date (30 June 2010).

Outcomes and estimation

Primary endpoint/Progression-Free Survival

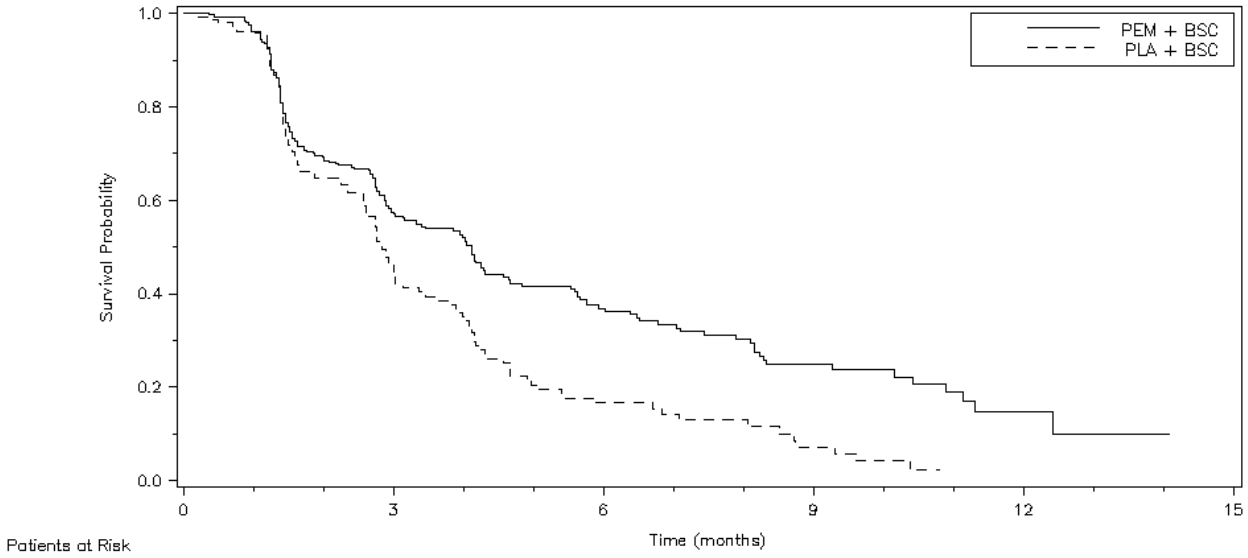
A total of 302 PFS events (pemetrexed: 184, 51.3%; placebo 118, 65.6%) had occurred at the time of database lock; 175 patients (48.7%) in the pemetrexed arm, and 62 patients (34.4%) in the placebo arm were censored for the PFS analysis. High-level PFS results are presented in the following table and figure.

Table 4: Investigator-assessed objective Progression-Free Survival-all randomised patients

	PFS	
	Pemetrexed N = 359	**Placebo N = 180**
Number (%) of events	184 (51.3)	118 (65.6)
Number (%) censored	175 (48.7)	62 (34.4)
25th percentile (95% CI)	1.51 (1.41 -1.87)	1.45 (1.41 -1.64)
Median PFS – months (95% CI)	4.11 (3.15 -4.57)	2.83 (2.60 -3.12)
75th percentile (95% CI)	8.31 (7.43 -11.14)	4.67 (4.07 -5.39)
Rate of patient with PFS of at least:		
3 months (95% CI)	0.57 (0.51 -0.63)	0.44 (0.35 -0.52)
6 months (95% CI)	0.37 (0.31 -0.43)	0.17 (0.10 -0.24)
9 months (95% CI)	0.25 (0.18 -0.32)	0.07 (0.03 -0.14)
12 months (95% CI)	0.15 (0.08 -0.23)	-
Log rank p-value	0.00006	
Hazard ratio (95% CI)[a]	0.62 (0.49 -0.79)	
Wald's p-value	0.00007	

Abbreviations: CI = confidence interval; HR = hazard ratio; N = total number of patients; PFS = progression-free survival. a Unadjusted HR and p-values from Cox model with treatment as the only cofactor. HR <1 favours pemetrexed study arm, HR >1 favours comparator.

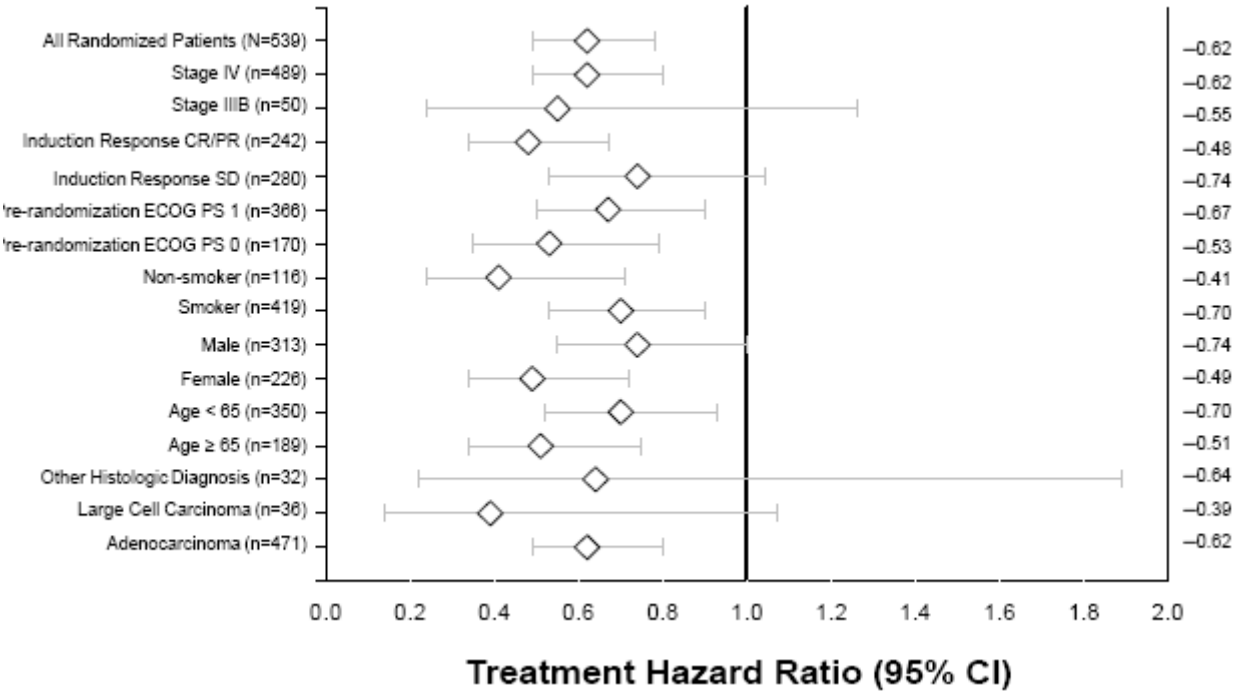
Figure 2: Kaplan-Meier graph of investigator-assessed objective Progression-Free Survival - all randomised patients



Abbreviations: BSC = best supportive care; n = number of patients at each time point; PEM = pemetrexed; PFS = progression– free survival; PLA = placebo.

PFS results in subgroups are presented in the following figure.

Figure 3: Investigator-assessed Progression-Free Survival hazard ratios (pemetrexed over placebo) in subgroups according to baseline characteristics - all randomised patients



Secondary endpoints

Overall Survival

PARAMOUNT included a pre-specified preliminary OS analysis at the time of the primary PFS data lock (30 June 2010) with a nominal alpha spending of 0.0001. The study was immature in terms of Overall Survival with high censoring rates (78.6% and 74.4% for the pemetrexed and placebo arms,

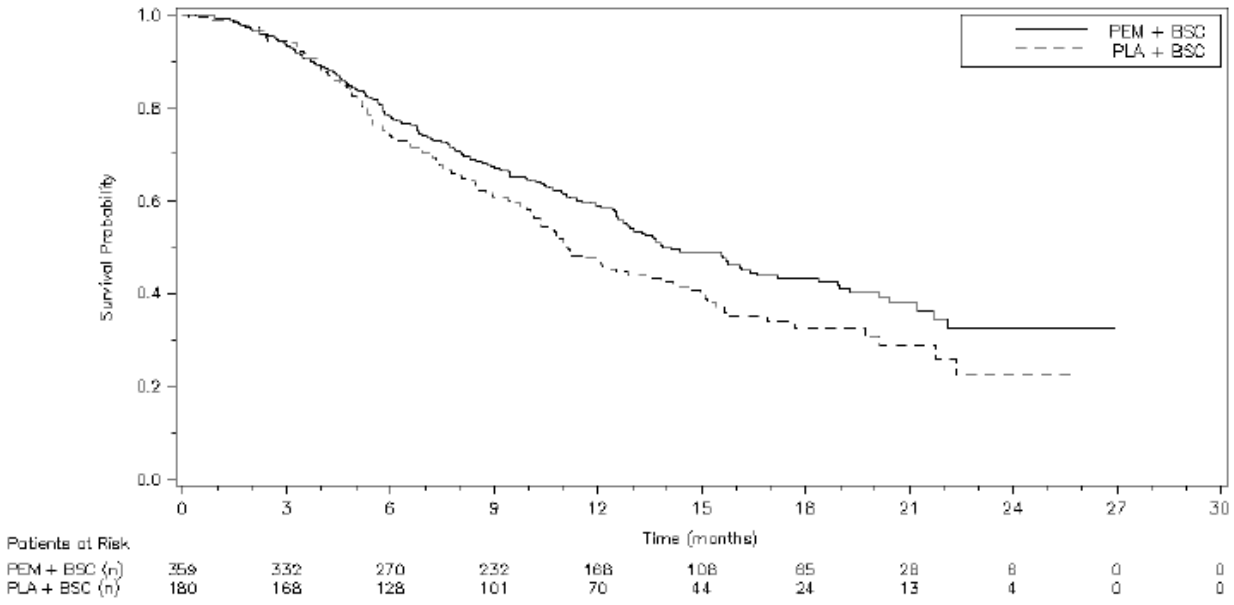
respectively). A second preliminary analysis of OS was conducted again with minimal alpha spending (0.0001) and a data lock of 06 June 2011. The median OS benefit for patients receiving pemetrexed (2.76 months, see Table 5 below) increased by 1.19 months from the first preliminary analysis, which had showed an OS benefit (median) of 1.57 months (data not shown). As with the first analysis, the results of the second analysis did not reach statistical significance. At the time of this second preliminary survival analysis, 48% of patients were alive on the pemetrexed arm versus 38% on the placebo arm, with a median follow-up of 11.04 months. There were 32 patients still on treatment (29 pemetrexed, 3 placebo). Per protocol, the final analysis of OS will take place after a minimum of 390 deaths have occurred among the randomised patients. The alpha level of the final OS analysis is 0.0498.

Table 5: Second preliminary Overall Survival analysis - all randomised patients

	OS	
	Pemetrexed N = 359	**Placebo N = 180**
Number (%) of events	188 (52.4)	111 (61.7)
Number (%) censored	171 (47.6)	69 (38.3)
Median OS – months (95% CI)	13.86 (12.75-16.59)	11.10 (10.09-14.19)
Hazard ratio (95% CI)[a]	0.78 (0.61 – 0.98)	
Log rank p-value[b]	0.0343	

Abbreviations: CI = confidence interval; HR = hazard ratio; N = number of randomised patients; OS = overall survival. [a]Unadjusted HR and p-values from Cox model with treatment as the only cofactor. An HR <1.0 favours the pemetrexed study arm; HR >1.0 favors the comparator. [b]Unadjusted log rank p-value.

Figure 4: Kaplan-Meier curve for second preliminary analysis of Overall Survival – all randomised patients



Abbreviations: BSC = best supportive care; n = number of patients at each time point; PEM = pemetrexed; PLA = placebo.

Objective tumour Response Rate

Results for tumour response based on investigator assessment are summarised in the following table. The tumour RR of the maintenance therapy (RR = CR + PR) was 4.2% in the pemetrexed arm and 1.1% in the placebo arm (p=.067).

Table 5: Summary of Investigator-assessed best tumour Response Rate – all randomised patients

Best Tumor Response	Number (%) of Patients (95% CI[a]) Pemetrexed (N = 359)	Placebo (N = 180)	p-Value[b]
CR, n (%)	3 (0.8)	0 (0.0)	0.554
(95% CI)	(0.17 – 2.42)		
PR, n (%)	12 (3.3)	2 (1.1)	0.157
(95% CI)	(1.74 – 5.77)	(0.13 – 3.96)	
SD, n (%)	149 (41.5)	59 (32.8)	0.060
(95% CI)	(36.36 – 46.79)	(25.98 – 40.15)	
PD, n (%)	87 (24.2)	66 (36.7)	0.003
(95% CI)	(19.89 – 29.01)	(29.62 – 44.16)	
Unknown (Not Applicable or Not Done) n (%)[c,d]	108 (30.1)	53 (29.4)	NE
(95% CI)	(25.38 – 35.12)	(22.90 – 36.68)	
Overall Response Rate (CR/PR), n (%)	15 (4.2)	2 (1.1)	0.067
(95% CI)	(2.36 – 6.80)	(0.13 – 3.96)	
Disease Control Rate (CR/PR/SD), n (%)	164 (45.7)	61 (33.9)	0.010
(95% CI)	(40.44 – 50.99)	(27.01 – 41.30)	

Abbreviations: CI= confidence interval, CR= complete response, N= number of randomised patients, n= number of patents in category, NE= not estmable, PR= partial response, RECIST= Response Evaluation Criteria in Solid Tumours, SD= stable disease. [a]confidence intervals based on exact binomial [b]p-value is from the Fisher exact test [c]progression was not documented or 1 or more target or non-target sites were not assessed [d]at the data cut-off (30 June 2010), 179 patients (pemetrexed: 136, placebo: 43) were still in the maintenance treatment phase.

The independent central review on 471 patients (316 patients in the pemetrexed arm and 156 patients in the placebo arm) yielded a tumour RR of 2.8% in the pemetrexed arm and 0.6% in the placebo arm (p=0.176). The independently reviewed Disease Control Rate (DCR) was 71.8% for patients receiving pemetrexed and 59.6% for patients receiving placebo (p=.009).

Patient-reported outcomes using the EuroQol 5-Dimensional Scale

Compliance during the maintenance treatment was 46.2% (163 of 359 patients completed the required questionnaire at each of their visits) for the pemetrexed arm and 44.1% (79 of 180 patients completed the required questionnaire at each of their visits) for the placebo arm. For the post-discontinuation visit, where the majority of worsening might have been anticipated, 43.9% of patients in the pemetrexed and 44.3% of patients in the placebo arm completed the EQ-5D. The most commonly reported reason for not completing the EQ-5D was failure by the investigative site to administer the questionnaire.

The EQ-5D United Kingdom (UK) population-based index score was generated from patient responses to items on mobility, self care, usual activities, pain/discomfort, and anxiety/depression. No statistical differences in the index scores were observed between the pemetrexed and placebo arms of the study. No statistical changes from baseline in index score at a given time point occurred over the course of maintenance therapy for the within-patient population regardless of treatment arm. At the discontinuation visit, the index score decreased from baseline for patients in both treatment arms. The index score of the pemetrexed arm was 0.77 at baseline and 0.66 at discontinuation (p<.001) and 0.79 at baseline and 0.70 at discontinuation (p=0.022) for placebo.

No statistical differences in VAS scores were observed between patients treated with pemetrexed and patients treated with placebo. Within both treatment arms, the VAS scores indicated an increasing trend toward "best-imaginable health state" with some significant increases from baseline at various time points. However, at discontinuation, patients receiving pemetrexed reported a significant

decrease in health state compared to baseline. Patients receiving placebo experienced a similar decrease at discontinuation. Based on the EQ-5D index scores and VAS scores, these results suggest that patients treated with pemetrexed did not experience worse health states over the course of maintenance therapy compared to patients treated with placebo.

Ancillary analyses

The MAH submitted a number of ancillary analyses for the primary endpoint of PFS including a covariate-adjusted analysis (data not shown) and an independent review of data. More specifically, the MAH established an independent review of PFS to assess the potential for investigator bias in the determination of PD between study arms. Of the 539 randomised patients with investigator assessed PFS, reviewable scans for 472 patients (87.4%, 316 in the pemetrexed arm and 156 in the placebo arm) were available for the independent review. The majority of unread scans were due to patients not completing 1 cycle of treatment by the data cut-off date (30 June 2010). Reasons for patients omitted from the independent review were balanced between study arms.

Independently assessed median PFS following induction therapy was 3.94 months in the pemetrexed arm and 2.6 months in the placebo arm. The treatment effect was statistically significant (HR = 0.64; 95% CI: 0.51 to 0.81; Wald's p =.00025).

The MAH also submitted sensitivity analyses for PFS using alternative censoring rules (data not shown).

Clinical studies in special populations

Subgroup analyses based on age and gender are presented in Figure 3. The majority of patients were Caucasian (94.6% of patients) and patient numbers from other ethnic origins were too small to draw meaningful conclusions.

Supportive studies

No supportive studies were submitted. The MAH made reference to the previously submitted JMEN (maintenance treatment after induction with a platinum doublet that did not include pemetrexed) and JMDB (first line treatment) trials, but no updated data/analyses from these studies were presented.

Discussion on clinical efficacy

Design and conduct of clinical studies

The present application for extension of the Alimta maintenance therapy indication after first line treatment of NSCLC is mainly based on the PARAMOUNT pivotal study. PARAMOUNT is the first NSCLC trial investigating pemetrexed only in patient who have a cancer with non-squamous histology. This can be considered as a consequence of preceding variation procedures limiting the original second line indication, and the first line (as well as the maintenance) indication of pemetrexed to specific NSCLC histologies.

The selection of placebo plus BSC as comparator is considered as acceptable. Of note, maintenance treatment has been challenged in similar settings with various agents, including pemetrexed, following a platinum doublet with gemcitabine, paclitaxel or docetaxel (JMEN, see CHMP AR on variation EMEA/H/C/000564/II/15), suggesting that prolonged therapy could be of benefit especially regarding PFS and possibly OS.

A total of 939 patients were enrolled, of which 539 (57.4%) were randomised 2:1 to study arms (pemetrexed arm N = 359; placebo arm N = 180) in the maintenance phase. All enrolled patients had non-squamous histology (no squamous patients were enrolled), and the majority of patients had adenocarcinoma (87.4%). The baseline patient demographic characteristics, disease characteristics, and prognostic factors were globally balanced between the study arms. There was however a slight imbalance in gender (more female patients in the pemetrexed arm).

The dose and schedule of pemetrexed were based on the results of studies JMEI (second line treatment) and JMEN. Therefore, patients received either 500 mg/m^2 pemetrexed or placebo.

Efficacy data and additional analyses

A total of 302 PFS events (pemetrexed: 184, 51.3%; placebo 118, 65.6%) had occurred at the time of database lock; 175 patients (48.7%) in the pemetrexed arm, and 62 patients (34.4%) in the placebo arm were censored for the PFS analysis.

This trial met its primary objective, as the analysis showed a statistically significant increase in investigator-assessed PFS for patients treated with maintenance pemetrexed. Median investigator-assessed PFS was 4.11 months (95% CI 3.15 to 4.57) in the pemetrexed arm and 2.83 months (95% CI 2.60 to 3.12) in the placebo arm. The estimated HR was 0.62 (95% CI: 0.49 to 0.79; Wald's p=0.00007).

These results correspond roughly with the results of trial JMEN (4.4 months for the Alimta arm and 1.8 months for the placebo arm, hazard ratio = 0.47 (95% CI = 0.37-0.60, p=0.00001; subgroup 'patients with NSCLC other than predominantly squamous cell histology').

A clear difference in PFS could be observed from the second month of treatment. This difference remained in favour of the pemetrexed arm up to 11 months. Although results are consistent in subgroups, there are some subgroups for which the 95% CI of HR includes 1, hence no difference could be confirmed statistically (see figure 3). However, few PFS events had occurred in these subgroups thus leading to wide 95% CIs.

Preliminary Overall Survival results at the time of the PFS analysis were immature with high censoring rates (78.6% and 74.4% for the pemetrexed and placebo arms, respectively). Data from a second preliminary OS analysis were considerably more mature and the censoring rate was already well below 50%, i.e. the number of events was higher than 50% (299 events) and median OS had already been reached. This new, second preliminary analysis showed an OS benefit for pemetrexed maintenance therapy vs. placebo with a difference in median OS of about 2.8 months, which did not reach statistical significance (p=0.0343) at the minimal (0.0001) alpha-level spent. An alpha spending of 0.0498 is still available for the final OS analysis.

Conclusions on the clinical efficacy

Taken together, these results are globally in line with those already submitted, in that pemetrexed monotherapy, administered as maintenance treatment after pemetrexed/cisplatin induction treatment has a significant effect on PFS.

3.2.3. Clinical safety

The safety analysis focused on the pivotal study H3E-EW-S124 (PARAMOUNT). The main focus in this section will be on the safety results from the maintenance treatment period. Where appropriate and meaningful, PARAMOUNT results are compared with results of 2 previously submitted studies (Study JMDB: pemetrexed plus cisplatin administered for the first-line treatment of advanced NSCLC; and

Study JMEN: pemetrexed administered as a single agent for the maintenance treatment of advanced NSCLC). Data (deaths, serious adverse events [SAEs], laboratory and non laboratory toxicities) from integrated safety results of the maintenance treatment period of PARAMOUNT and of the JMEN study are also described.

Patient exposure

A total of 1622 cycles of pemetrexed were administered to 333 patients in the pemetrexed arm, and 698 cycles of placebo were administered to 167 patients in the placebo arm. In addition, 23.4% of patients in the pemetrexed arm completed >6 cycles of maintenance (representing a minimum of 10 total cycles of pemetrexed treatment [4 cycles of induction plus 6 cycles of maintenance]) compared with only 13.9% of patients in the placebo arm.

Table 7: **Number of chemotherapy cycles (maintenance), all randomised patients**

Parameter	Pemetrexed Plus BSC (N=359) n (%)	Placebo Plus BSC (N=180) n (%)	p-value
Number of patients <= 6 cycles	**275 (76.6)**	**155 (86.1)**	**.009**
Number of patients > 6 cycles	**84 (23.4)**	**25 (13.9)**	
Total number of cycles received	**1622**	**698**	

A comparison of exposure in the two maintenance trials (PARAMOUNT and JMEN) is shown in the following two tables.

Table 8: Patient exposure to maintenance treatment; all randomised patients; PARAMOUNT and JMEN

	PARAMOUNT	Study JMEN
Statistic	Pemetrexed (N = 359)	Pemetrexed (N = 441)
Median	4.0	4.0
Mean	4.9	6.1
Standard Deviation	3.8	5.7
Range	0 - 19	0 - 34
n (%) completing >6 cycles	84 (23.4)	130 (29.5)

Abbreviations: N = total number of randomized patients; n = number of patients.

Table 9: Mean doses and dose intensity of maintenance treatment; all randomised patients; PARAMOUNT and JMEN

	PARAMOUNT	Study JMEN
	Pemetrexed (N=359)	Pemetrexed (N = 441)
Planned mean weekly dose (mg/m^2)	166.7	166.7
Actual mean weekly dose (mg/m^2)	157.9	160.2
Dose intensity (%)[a]	94.8	96.1

Abbreviation: N = total number of randomized patients.

[a] (Actual mean weekly dose ÷ planned mean weekly dose) × 100

During induction treatment, 179 patients (19.1%) had dose delays due to adverse events, 389 patients (41.4%) for scheduling conflict and 6 (0.6%) due to inadequate vitamin supplementation. During maintenance treatment, 72 patients (20.1%) in pemetrexed arm and 26 (14.4%) in the

placebo arm had dose delays due to adverse events, 179 (49.9%) vs. 66 (36.7%) due to scheduling conflict and 1 in each arm due to inadequate vitamin supplementation.

During induction treatment, 62 (6.6%) of patients had dose reductions due to AE. During maintenance treatment, 11 (3.1%) patients in the pemetrexed arm had dose reduction compared to 1 (0.6%) patient in the placebo arm. All the dose reductions were due to Adverse Events.

Adverse events

An overview of adverse events observed in the induction and maintenance phase of the PARAMOUNT trial compared with studies JMDB and JMEN, as appropriate, is presented in the following two tables.

Table 10: Overview of Adverse Events on induction treatment in PARAMOUNT and JMDB

	PARAMOUNT		Study JMDB
	All Randomized Patients	All Enrolled Patients	All Randomized and Treated Patients
Adverse events during the safety reporting period[a, b]	Pemetrexed plus Cisplatin (N = 539) n (%)	Pemetrexed plus Cisplatin (N = 939) n (%)	Pemetrexed plus Ciplatin (N = 839, n (%)
Patients with ≥1 TEAE	449 (83.3)	771 (82.1)	812 (96.8)
Possibly related to study drug	397 (73.7)	643 (68.5)	751 (89.5)
Patients with ≥1 SAE	84 (15.6)	247 (26.3)	294 (35.0)
Possibly related to study drug	46 (8.5)	133 (14.2)	139 (16.6)
Patients who discontinued due to AE		88 (9.4)	95 (11.3)
Possibly related to study drug		51 (5.4)	72 (8.6)
Patients who discontinued due to SAE		59 (6.3)	30 (3.6)
Possibly related to study drug		31 (3.3)	15 (1.8)
Patients who died on therapy		56 (6.0)	63 (7.5)
Possibly related to study drug		11 (1.2)	9 (1.1)
Patients who died within 30 days of last dose of study drug			13 (1.5)
Possibly related to study drug			0 (0.0)

Abbreviations: AE= adverse event, N= number of patients, n= number of patients in the specific category, SAE= serious adverse event, TEAE= treatment-emergent adverse event, [a]While on study treatment for PARAMOUNT. Patients may be counted in more than 1 category, [b]While on study treatment or within 30 days of discontinuation of study treatment for JMDB. Patients may be counted in more than 1 category, Empty cells correspond to situations non-applicable for the relevant category

Table 11: Overview of Adverse Events on maintenance treatment in PARAMOUNT and JMEN; all randomised patients

	PARAMOUNT		Study JMEN[c]	
Adverse events during the safety reporting period[a]	Pemetrexed (N = 359) n (%)	Placebo (N = 180) n (%)	Pemetrexed (N = 441) n (%)	Placebo (N = 222) n (%)
Patients with ≥1 TEAE	231 (64.3)[d]	96 (53.3)[d]	375 (85.0)	179 (80.6)
Possibly related to study drug	155 (43.2)[d]	45 (25.0)[d]	278 (63.0)[d]	78 (35.1)[d]
Patients with ≥1 SAE	68 (18.9)	22 (12.2)	71 (16.1)	31 (14.0)
Possibly related to study drug	32 (8.9)[d]	5 (2.8)[d]	19 (4.3)[d]	0 (0.0)[d]
Patients who discontinued due to AE	36 (10.0)[d]	9 (5.0)[d]	26 (6.6)[d]	5 (2.3)[d]
Possibly related to study drug	19 (5.3)	6 (3.3)	17 (3.9)	3 (1.4)
Patients who discontinued due to SAE	14 (3.9)	3 (1.7)	9 (2.0)	2 (0.9)
Possibly related to study drug	7 (1.9)	2 (1.1)	1 (0.2)	0 (0.0)
Patients who died on therapy	7 (1.9)	3 (1.7)	4 (0.9)	6 (2.7)
Possibly related to study drug	1 (0.3)	1 (0.6)	0 (0.0)	0 (0.0)
Patients who died within 30 days of last study drug dose	1 (0.3)	2 (1.1)	7 (1.6)	4 (1.8)
Possibly related to study drug	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Patients who died > 30 days of last study drug dose	69 (19.2)	41 (22.8)	177 (40.1)	101 (45.5)
Possibly related to study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AE= adverse event, N= number of patients, n= number of patients in the specific category, SAE= serious adverse event, TEAE= treatment-emergent adverse event, [a]While on study treatment or within 30 days of

discontinuation of study treatment. Patients may be counted in more than 1 category, [c]The JMEN data presented are based on the primary database lock (cut-off date of 17 August 2007), [d]Difference is statistically significant (Fisher's exact test p≤0.05).

In the induction phase, the most commonly reported induction treatment-related TEAEs (reported in ≥5% of patients) were: nausea (36.2%), vomiting (21.6%), neutropenia (16.3%), fatigue (14.9%), anaemia (14.3%), asthenia (11.8%), decreased appetite (9.5%), diarrhoea (8.8%), constipation (8%), and mucosal inflammation (5.5%).

A summary of treatment-related AEs (Adverse Drug Reactions, ADRs) occurring in at least 1% of patients in the induction phase of the PARAMOUNT trial and compared to the JMDB trial is presented in the following table.

Table 12: Adverse Events possibly related to study drug occurring in ≥1% in PARAMOUNT (induction treatment) with corresponding percentages from JMDB, all enrolled patients (PARAMOUNT) and all randomised and treated patients (JMDB)

	Number (%) of All Enrolled Patients		Number (%) of All Randomized and Treated Patients	
	PARAMOUNT		Study JMDB	
	Pemetrexed plus Cisplatin (N = 939)		Pemetrexed plus Cisplatin (N = 839)	
Toxicity	**All Grades**	**Grade 3/4/5**	**All Grades**	**Grade 3/4**
Patients with ≥ 1 nonlaboratory toxicity[c]	**574 (61.1)**	**145 (15.4)**	**700 (83.4)**	**180 (21.5)**
Vomiting	204 (21.7)	34 (3.6)	333 (39.7)	51 (6.1)
Nausea	342 (36.4)	29 (3.1)	471 (56.1)	60 (7.2)
Fatigue (asthenia, lethargy, malaise)	259 (27.6)	27 (2.9)	358 (42.7)	56 (6.7)
Diarrhea	83 (8.8)	13 (1.4)	104 (12.4)	11 (1.3)
Febrile neutropenia	13 (1.4)	13 (1.4)	12 (1.4)	11 (1.3)
Anorexia	91 (9.7)	9 (1.0)	223 (26.6)	20 (2.4)
Dehydration	13 (1.4)	9 (1.0)	30 (3.6)	10 (1.2)
Renal failure	10 (1.1)	9 (1.0)	9 (1.1)	5 (0.6)
Thrombosis/thrombus/embolism	9 (1.0)	9 (1.0)	4 (0.5)	4 (0.5)

Abbreviations: CTC= Common Toxicity Criteria, CTCAE= Common Terminology Criteria for Adverse Events, N= total number of patients, n= number of patients in the specific category

In the maintenance phase and in both treatment arms, the most commonly reported possibly study-drug-related TEAEs (reported in ≥5% of patients) were anaemia, asthenia, fatigue, nausea, and neutropenia. Patients receiving pemetrexed experienced a significantly greater number of the following possibly study-drug related TEAEs: anaemia (7.5% versus 1.1%, p<.001), neutropenia (4.5% versus 0.6%, p=.016), leukopenia (3.3% versus 0%, p=.011), increased lacrimation (2.5% versus 0%, p=.033), nausea (5% versus 1.1%, p=.028), and asthenia (7.5% versus 1.1%, p<.001).

All-grade and grade 3/4/5 possibly treatment-related AEs (Adverse Drug Reactions, ADRs) in the maintenance phase of the PARAMOUNT trial and compared to the JMEN trial are presented below.

Table 13: Adverse Events possibly related to study drug in PARAMOUNT (maintenance treatment) with corresponding percentages from JMEN, all randomised patients

	Number (%) of Patients							
	PARAMOUNT				Study JMEN			
	Pemetrexed (N = 359)		Placebo (N = 180)		Pemetrexed (N = 441)		Placebo (N = 222)	
	All Grades	Grade 3/4/5[a]	All Grades	Grade 3/4/5[a]	All Grades	Grade 3/4[a]	All Grades	Grade 3/4[a]
Patients with ≥1 non-laboratory toxicity[b]	146 (40.7)[c]	32 (8.9)	49 (27.2)[c]	8 (4.4)	253 (57.4)[c]	47 (10.7)[c]	63 (28.4)[c]	3 (1.4)[c]
Fatigue (asthenia, lethargy, malaise)	59 (16.4)	15 (4.2)[c]	19 (10.6)	1 (0.6)[c]	103 (23.4)	19 (4.3)[c]	22 (9.9)	1 (0.5)[c]
Nausea	39 (10.9)[c]	1 (0.3)	4 (2.2)[c]	0 (0.0)	82 (18.6)[c]	3 (0.7)	10 (4.5)[c]	1 (0.5)
Vomiting	21 (5.8)[c]	0 (0.0)	3 (1.7)[c]	0 (0.0)	37 (8.4)[c]	0 (0.0)	3 (1.4)[c]	0 (0.0)
Mucositis/stomatitis[e,j]	18 (5.0)	1 (0.3)	4 (2.2)	0 (0.0)	30 (6.8)	3 (0.7)	3 (1.4)	0 (0.0)
Edema[f,j]	17 (4.7)	0 (0.0)	6 (3.3)	0 (0.0)	17 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)
Anorexia	14 (3.9)	1 (0.3)	2 (1.1)	0 (0.0)	80 (18.1)[c]	7 (1.6)	11 (5.0)[c]	0 (0.0)
Pain, any event	13 (3.6)	3 (0.8)	3 (1.7)	0 (0.0)	40 (9.1)	2 (0.5)	13 (5.9)	0 (0.0)
Infection[a,g,j]	12 (3.3)	4 (1.1)	3 (1.7)	2 (1.1)	19 (4.3)	4 (0.9)	4 (1.8)	0 (0.0)
Diarrhea	10 (2.8)	0 (0.0)	3 (1.7)	0 (0.0)	21 (4.8)	2 (0.5)	6 (2.7)	0 (0.0)
Neuropathy: sensory	10 (2.8)	1 (0.3)	10 (5.6)	1(0.6)	38 (8.6)[c]	3 (0.7)	9 (4.1)[c]	0 (0.0)
Watery eye (epiphora, tearing)	9 (2.5)	0 (0.0)	1 (0.6)	0 (0.0)	8 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	8 (2.2)	0 (0.0)	5 (2.8)	0 (0.0)	18 (4.1)	3 (0.7)	6 (2.7)	0 (0.0)
Fever (in the absence of neutropenia)	8 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	13 (2.9)[c]	0 (0.0)	0 (0.0)[c]	0 (0.0)
Dry eye syndrome	6 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile neutropenia	6 (1.7)	6 (1.7)	0 (0.0)	0 (0.0)	4 (0.9)	3 (0.7)	0 (0.0)	0 (0.0)
Glomerular filtration rate	6 (1.7)	0 (0.0)	3 (1.7)	0 (0.0)	5 (1.1)	3 (0.7)	1 (0.5)	0 (0.0)
Rash[i,j]	6 (1.7)	0 (0.0)	2 (1.1)	0 (0.0)	55 (12.5)	1 (0.2)	11 (5.0)	0 (0.0)
Dizziness	5 (1.4)	1 (0.3)	2 (1.1)	0 (0.0)	7 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea (shortness of breath)	4 (1.1)	1 (0.3)	2 (1.1)	0 (0.0)	7 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Neurology – Other	4 (1.1)	0 (0.0)	2 (1.1)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Ocular surface disease	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	7(1.6)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy: motor	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pain neurology – Head/headache	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.8)	0 (0.0)	4 (1.8)	0 (0.0)
Taste alteration (dysgeusia)	4 (1.1)	0 (0.0)	2 (1.1)	0 (0.0)	7 (1.6)	0 (0.0)	1 (0.5)	0 (0.0)
Hair loss/alopecia (scalp or body)	3 (0.8)	0 (0.0)	4 (2.2)	0 (0.0)	16 (3.6)[c]	0 (0.0)	2 (0.9)[c]	0 (0.0)
Dry mouth/salivary gland (xerostomia)	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.8)	0 (0.0)	2 (0.9)	0 (0.0)
Gastritis (including bile reflux gastritis)	3 (0.8)	1 (0.3)	1 (0.6)	0 (0.0)	--	--	--	--
Auditory/Ear – Other	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	--	--	--	--
Blood/Bone Marrow – Other	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	2 (0.6)	2 (0.6)	1 (0.6)	0 (0.0)	2 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
Dysphagia (difficulty swallowing)	2 (0.6)	2 (0.6)	1 (0.6)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Gastrointestinal - Other	2 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)
Metabolic Laboratory - Other	2 (0.6)	0 (0.0)	1 (0.6)	0 (0.0)	10 (2.3)[c]	0 (0.0)	0 (0.0)[c]	0 (0.0)
Hepatobiliary/Pancreas – Other	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Phlebitis(including superficial thrombosis)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	--	--	--	--
Renal failure	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
Thrombosis/thrombus/embolism	2 (0.6)[i]	2 (0.6)[i]	1 (0.6)	1 (0.6)	--	--	--	--
Tinnitus	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular arrhythmia Ventricular tachycardia	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	--	--	--	--
Allergic reaction/hypersensitivity	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Allergic rhinitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	--	--	--	--
Constitutional Symptoms – Other	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	--	--	--	--
Dry skin	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Flatulence	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Flushing	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (1.6)	0 (0.0)	3 (1.4)	0 (0.0)
Flu-like syndrome	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	1 (0.5)	0 (0.0)
Heartburn/dyspepsia	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	6 (1.4)	0 (0.0)	3 (1.4)	0 (0.0)
Hemorrhage, GU Urinary NOS	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)_	0 (0.0)

	Number (%) of Patients							
	PARAMOUNT				Study JMEN			
	Pemetrexed (N = 359)		Placebo (N = 180)		Pemetrexed (N = 441)		Placebo (N = 222)	
	All Grades	Grade 3/4/5[a]	All Grades	Grade 3/4/5[a]	All Grades	Grade 3/4[a]	All Grades	Grade 3/4[a]
Hemorrhage, pulmonary/upper respiratory nose	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.7)	1 (0.2)	0 (0.0)	0 (0.0)
Hemorrhoids	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	--	--	--	--
Hypotension	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	--	--	--	--
Insomnia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Joint-function	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	--	--	--	--
Mood alteration Depression	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle weakness, generalized or specific area (not due to neuropathy) Whole body/generalized	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	10 (2.3)	0 (0.0)	1 (0.5)	0 (0.0)
Obstruction, GI	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	--	--	--	--
Pruritus/itching	1 (0.3)	0 (0.0)	2 (1.1)	0 (0.0)	14 (3.2)	2 (0.5)	2 (0.9)	0 (0.0)
Renal genitourinary – Other	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.0)[c]	1 (0.2)	0 (0.0)[c]	0 (0.0)
Sweating (diaphoresis)	1 (0.3)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Syncope (fainting)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	--	--	--	--
Weight gain	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Weight loss	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	3 (0.7)	1 (0.2)	2 (0.9)	0 (0.0)
Death not associated with CTCAE term Death NOS[a]	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	--	--	--	--
Dermatology/Skin – Other	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	4 (0.9)	2 (0.5)	0 (0.0)	0 (0.0)
Hemorrhage, pulmonary/upper respiratory Respiratory tract NOS	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	--	--	--	--
Hypertension	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	--	--	--	--
Injection site reaction/extravasation changes	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle weakness, generalized or specific area (not due to neuropathy) Extremity – lower	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
Speech impairment (e.g., dysphasia or aphasia)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	--	--	--	--
Uric acid, serum-high (hyperuricemia)	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)
Vision-blurred vision	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; N = total number of randomized patients; n = number of patients in the specified category; NOS = not otherwise specified.

a There were 2 possibly study-drug-related Grade 5 nonlaboratory toxicities (deaths) in PARAMOUNT during the maintenance treatment period: 1 on pemetrexed ('Infection [clinical/microbio] – Gr 3/4 neutrophils – Pulmonary/Upper respiratory –Lung [pneumonia]') and 1 on placebo ('Death not associated with CTCAE term Death NOS'). There were no drug-related Grade 5 nonlaboratory toxicities in Study JMEN.

b PARAMOUNT toxicities were reported using CTCAE Version 3.0 (NCI 2006). Study JMEN toxicities were reported using CTC Version 3.0 (NCI 2003).

c Difference between treatment arms is statistically significant (Fisher exact test $p \leq 0.05$).

e Combined term includes Mucositis/stomatitis (clinical exam) Anus, Mucositis/stomatitis (clinical exam) Oral cavity, Mucositis/stomatitis (functional/symptomatic) Esophagus, Mucositis/stomatitis (functional/symptomatic) Oral cavity, Mucositis/stomatitis (functional/symptomatic) Stomach, and Mucositis/stomatitis (functional/symptomatic) Trachea.

f Combined term includes Edema: Limb and Edema: head and neck.

g Combined term includes infection terms shown in the INFECTION category excluding febrile neutropenia.

h Combined term includes Rash/desquamation, Rash: erythema multiforme (for example, Stevens-Johnson syndrome, toxic epidermal necrolysis), Rash: hand-foot skin reaction, and Rash: acne/acneiform.

i Both cases were pulmonary embolism.

j Study JMEN data presented is based on the output from the integrated safety analyses; statistical comparisons are not provided for Study JMEN.

Note: A patient randomized to maintenance treatment experienced a possibly study-drug-related Grade 5 nonlaboratory toxicity (endocarditis), which was classified as a poststudy event. Event is not summarized in the toxicity table.

Of particular interest, the overall incidence of pulmonary embolism (PE) in the maintenance pemetrexed arm in PARAMOUNT was low, similar between pemetrexed and placebo [0.8% (3/359) in the maintenance pemetrexed arm vs 1.7% (3/180) on placebo], and comparable with Study JMEN [0.2% (1/441) on maintenance pemetrexed and 0.5% (1/222) on placebo]. In PARAMOUNT, the reporting rate for all PE events possibly related to study treatment was 0.6% (2/359) in the maintenance pemetrexed arm versus 0.6% (1/180) on placebo. In JMEN, there were no cases of PE possibly related to study treatment in either treatment arm. Finally, PARAMOUNT included induction treatment with pemetrexed plus cisplatin and the incidence of PE during induction was 4.4% (41/939) for all events and 0.9% (8/939) for events possibly related to study treatment.

Serious adverse event/deaths/other significant events

Deaths

In both induction and maintenance phases, deaths were categorised as 'regardless of causality' or 'possibly related to study drug'.

In the induction phase, of all enrolled patients who were treated with at least 1 dose of pemetrexed or cisplatin (N = 939), 56 (6%) on-study deaths occurred. There were 11 possibly study drug-related deaths. The primary events included febrile neutropenia (2 events), diarrhoea, intestinal obstruction, large intestine perforation, neutropenic colitis, renal failure, cerebrovascular accident, multi-organ failure, lung infection and acute renal failure. Of all enrolled, but not randomised patients (N=400), 7 deaths (1.8%) occurred within 30 days of the last dose of induction treatment; of these, 5 were due to study disease, 1 was due to an AE (cerebro-vascular accident), and 1 was a possibly study drug-related death due to dyspnoea. Deaths >30 days after last dose of induction treatment occurred in 184 (46.0% of 400) patients treated with pemetrexed plus cisplatin. With the exception of 7 deaths due to AEs, the cause of death for these patients was listed as disease progression.

In the maintenance phase, among all randomised patients (N = 539), 10 on-study deaths occurred (7 [1.9%] in the pemetrexed arm and 3 [1.7%] in the placebo arm). Of these, 5 were attributed to disease progression (4 in the pemetrexed arm and 1 in the placebo arm). Two deaths (1 in each treatment arm) were AEs considered by the investigator to be possibly related to study drug (pneumonia in 1 patient treated with pemetrexed, sudden death in 1 patient treated with placebo). The remaining 3 deaths (2 on pemetrexed, 1 on placebo) were caused by AEs not attributed to study drug. Moreover, there were 3 additional deaths within 30 days of the last administered maintenance dose (1 in the pemetrexed arm and 2 in the placebo arm). The pemetrexed death was due to possibly study drug-related endocarditis. The placebo deaths were due to disease progression. Deaths >30 days of the last dose of maintenance treatment occurred in 69 pemetrexed-treated and 41 placebo-treated patients, with the cause of death for the majority of the patients listed as disease progression.

Compared with the 13 deaths in PARAMOUNT during maintenance treatment and within 30 days of last dose, there were 21 deaths during the same period in Study JMEN. In Study JMEN, 11 (2.5%) deaths were in the pemetrexed arm and 10 (4.5%) were in the placebo arm, and none were considered possibly related to study drug. Of the 309 deaths reported in JMEN, there were 21 deaths (11 [2.5%] in the pemetrexed arm and 10 [4.5%] in the placebo arm) that occurred while patients were on study or within 30 days of their last study dose. The remaining 278 deaths occurred >30 days after the last study dose. The deaths were primarily related to disease progression.

Overall, there were no significant differences in the reasons for deaths between the pemetrexed and placebo arms for the integrated analysis of the maintenance treatment period from PARAMOUNT and Study JMEN, except for deaths due to disease progression >30 days after last dose (34.5% pemetrexed [N = 800] versus 41.0% placebo [N = 402], p=0.03).

SAEs

In PARAMOUNT, the most common SAEs possibly related to induction treatment were vomiting and nausea, occurring in 2.6% and 2.3% of patients, respectively. Eleven (1.2%) patients experienced renal failure SAEs (renal acute failure, renal failure) possibly related to induction treatment.

Similarly in JMDB, vomiting (4.1%), nausea (3.6%), and anaemia (2.6%) were the most common study drug-related SAEs, with 1.4% patients with SAEs related to renal failure (acute renal failure, acute pre-renal failure, and renal failure).

In the maintenance phase of the PARAMOUNT study, 8.9% of patients in the pemetrexed arm and 2.8% of patients in the placebo arm experienced a SAE that was considered possibly related to the study drug (p=.007). No significant differences were observed in the incidence of any individual event. The most common SAEs reported in the pemetrexed arm were anaemia (2.2%), followed by febrile neutropenia (1.4%).

The overall incidence of drug-related SAEs in the pemetrexed arm of PARAMOUNT (8.9%) was numerically higher than in JMEN (4.3%). The magnitude of change between the pemetrexed and placebo arms was similar between the two studies. Consistent with PARAMOUNT results, anaemia (1.4%) was the most frequently reported SAE in JMEN. In the integrated analysis of the maintenance treatment period from PARAMOUNT and JMEN, 6.6% of patients in the pemetrexed arm (N = 800) and 1.2% of patients in the placebo arm (N = 402) experienced a SAE that was considered possibly related to the study drug (p<.01). Individual SAE terms that occurred significantly higher in the combined pemetrexed arm compared to the combined placebo arm included anaemia (1.8% versus 0%; p<.01) and febrile neutropenia (1.1% versus 0%; p=.03).

Laboratory findings

In the induction phase of the PARAMOUNT trial, there was only study-drug-related Grade 5 laboratory toxicity (death), i.e. increased creatinine which was reported as a primary event of acute renal failure. Possibly study-drug-related Grade 3/4 laboratory toxicities reported in ≥1% of patients in PARAMOUNT included neutrophils/granulocytes, haemoglobin, platelets, and leukocytes. The overall incidence of Grade 3/4/5 laboratory toxicities (all enrolled patients) possibly related to pemetrexed plus cisplatin was lower in PARAMOUNT (13.7%) compared to JMDB (22.6%).

In the maintenance phase of the PARAMOUNT trial, there were no possibly study drug-related Grade 5 laboratory toxicities (deaths) reported in either study. Overall, toxicity was low on both arms in the maintenance treatment period, such that there were few differences between the treatment arms and few patients experiencing clinically important AEs. Results in the pemetrexed arm of PARAMOUNT were consistent with the laboratory toxicities seen in Study JMEN. Hemoglobin and neutrophils/granulocytes were the most common possibly study-drug-related Grade 3/4 hematologic toxicities in the pemetrexed arm of both studies, with incidences higher in PARAMOUNT than in JMEN. In the integrated analysis of the maintenance treatment period from PARAMOUNT and JMEN, the overall incidence of Grade 3/4 laboratory toxicities possibly related to study treatment was significantly different in the pemetrexed arm compared to the placebo arm (7.5% versus 1.5%, p<0.01). The following individual possibly study-drug-related Grade 3/4 laboratory toxicities were reported in significantly more patients on pemetrexed versus placebo treatment arm: haemoglobin (3.5% versus 0.5%; p<0.01), leukocytes (1.6% versus 0.2%; p = 0.04), neutrophils/granulocytes (3.3% versus 0%; p<0.01), and platelets (1.6% versus 0.2%; p = 0.04).

Safety in special populations

The MAH provided safety analyses from the PARAMOUNT study based on age (<65 years and ≥years), gender (male, female) and ethnic origin (Asian, Black/African American, Caucasian) and comparisons of the induction and maintenance phase of this study with studies JMDB and JMEN, accordingly. The safety profile was similar in the age and gender subgroups across the various trials and no age- or gender-specific differences in toxicity were noted (data not shown). No meaningful conclusions could be made for ethnic subgroups, as the number of non-Caucasian patient was minimal.

Discontinuation due to adverse events

Fifty-one (5.4%) patients discontinued induction treatment because of possibly study-drug-related AEs, the majority (16 [1.7%]) were attributable to a decrease in renal function. Similarly, renal toxicities were the most common causes of possibly study-drug-related discontinuation in Study JMDB (possibly drug-related events of blood creatinine, increased blood creatinine, decreased creatinine clearance, renal failure, acute renal failure, renal impairment, or renal infarct caused discontinuations for 32 patients [3.8%] on the pemetrexed plus-cisplatin arm).

Nineteen (5.3%) patients in the pemetrexed arm and 6 (3.3%) patients in the placebo arm discontinued study therapy because of study-drug-related AEs. The difference between the 2 treatment arms was not significant and no significant differences were observed between the study arms in the incidence of individual study-drug-related AEs leading to discontinuation. The majority of non-serious drug-related AEs causing discontinuation (6 patients) from the PARAMOUNT pemetrexed arm were attributed to asthenia, fatigue, and renal failure (2 patients each). Seven patients discontinued from pemetrexed therapy because of study-drug-related SAEs (1 patient each, bone marrow failure, anaemia, thrombocytopenia, arrhythmia, odynophagia, febrile neutropenia, and pneumonia). Two patients discontinued from placebo therapy because of study-drug-related SAEs [sudden death (1) and dehydration (1)].

The type of possibly study-drug-related AEs causing discontinuation in PARAMOUNT during maintenance treatment was similar to that seen in trial JMEN. In trial JMEN, 3.8% of pemetrexed-treated patients discontinued because of drug-related AEs (both serious and nonserious) and 0.2% discontinued because of drug-related SAEs.

Post marketing experience

It is estimated that approximately 491,368 patients have been exposed to pemetrexed worldwide since it was first approved on 04 February 2004 to 31 August 2010 if the patients received an average of 4 cycles and 655,158 patients if they received an average of 3 cycles.

A total of 2497 spontaneous AE case reports containing 6197 events were identified. Of the 6197 AEs, 3096 were classified as serious (1649 listed, 1477 unlisted) and 3101 were nonserious (1866 listed, 1235 unlisted).

The MedDRA system organ classes (SOCs) with the highest proportion of events were General Disorders and Administration Site Conditions, Skin and Subcutaneous Tissue Disorders, Gastrointestinal Disorders, and Blood and Lymphatic System Disorders.

Overall, the most frequently reported unlisted events (>1%) were malignant neoplasm progression (3.31%; 205/6197), dyspnoea (1.18%; 73/6197), and death (1.02%; 63/6197).

A review of the 368 fatal case reports, including the 63 reports with death coded as an event, did not identify any significant new safety information. There were no new trends associated with non-serious and serious events that were already listed in the Core Company Data Sheet (CCDS) for pemetrexed.

In 19.1% (476/2497) of case reports, the patient received a platinum agent (either cisplatin or carboplatin) in combination with pemetrexed as part of combination chemotherapy treatment.

Discussion and conclusions on clinical safety

In the pivotal study PARAMOUNT, 56 deaths occurred during induction treatment of which 11 were due to study drug-related AE. Among the 15 death due to unrelated AE, 4 were secondary to pulmonary embolism. Comparison of data from the PARAMOUNT and JMDB studies showed a higher toxicity in the

JMDB study. Increased toxicity could be explained by a higher exposure to pemetrexed-cisplatin (up to 6 cycles) during induction in JMDB in comparison to the PARAMOUNT induction treatment (4 cycles).

However, no new safety signal emerged from the comparison of the PARAMOUNT induction treatment and JMDB. Overall, the safety results observed in the PARAMOUNT study are consistent with the known safety profile of pemetrexed.

During maintenance treatment, there was no difference between placebo and pemetrexed arms in term of deaths.

As expected, more patients in the pemetrexed arm had dose delays due to adverse events (20.1%) in comparison to the placebo arm (14.4%). The most common reasons for dose delays in active arm were AEs related to haematotoxicity (anaemia, neutropenia, leucopenia, haemoglobin decreased).

Similarly, dose reductions were more frequent in the pemetrexed arm (3.1%) in comparison to the placebo arm (0.6%). All the dose reductions were due to AEs.

During maintenance treatment, frequencies of SAEs and related SAEs were higher in the pemetrexed arm. However, due to the small number of SAEs, the difference between both arms was non-significant. Overall, 14 patients (3.9%) in the pemetrexed arm and 3 (1.7%) in the placebo arm discontinued treatment due to SAEs.

In addition, pulmonary embolism (PE) has been included in the proposed SmPC as a newly identified Adverse Drug Reaction (ADR).

3.2.4. Risk Management Plan

The MAH considered that no new clinical or non-clinical safety concern was identified in the pivotal PARAMOUNT study, hence the Risk Management Plan does not require to be updated within this application and the current Risk Management Plan (Revision 4), submitted together with PSUR 9 in April 2011, is up-to-date.

As mentioned immediately above, several cases of pulmonary embolism have been reported as Adverse Drug Reactions in the PARAMOUNT study, among which 4 led to death. Until now, this risk was unexpected, so that Pulmonary Embolism was added in section 4.8 of the SmPC. On the other hand, pulmonary embolism is not addressed in the current version 4 of the Risk Management Plan, submitted together with PSUR 9 in April 2011. The Risk Management Plan will be updated accordingly at the next update in the first quarter of 2012.

3.3. Benefit-Risk balance

Benefits

- Beneficial effects

The present application for extension of the existing Alimta maintenance indication after first line treatment of NSCLC is mainly based on the PARAMOUNT pivotal study, which is a multicentre, randomised, double-blind, placebo-controlled phase III study designed to compare maintenance therapy with pemetrexed plus BSC versus placebo plus BSC in terms of objective PFS time in patients with Stage IIIB or Stage IV non-squamous NSCLC whose disease has not progressed during 4 cycles of pemetrexed and cisplatin induction chemotherapy.

This trial met its primary objective, as the analysis showed a statistically significant (log rank p=.00006) increase in investigator-assessed PFS for patients treated with maintenance pemetrexed.

Median investigator-assessed PFS was 4.11 months (95% CI 3.15 to 4.57) in the pemetrexed arm and 2.83 months (95% CI 2.60 to 3.12) in the placebo arm.

The HR was 0.62 (95% CI: 0.49 to 0.79; Wald's p=.00007) which represents a 38% reduction in the risk of disease progression for patients receiving pemetrexed. Independently assessed median PFS following induction therapy was 3.94 months in the pemetrexed arm and 2.6 months in the placebo arm. The treatment effect was statistically significant (HR = 0.64; 95% CI: 0.51 to 0.81; Wald's p =.00025).

A clear difference in PFS could be observed from the second month of treatment. This difference remained in favour of the pemetrexed arm up to 11 months. Although results are consistent in subgroups, there are some subgroups for which the 95% CI of HR includes 1, hence no difference could be confirmed statistically (see figure 3). However, few PFS events had occurred in these subgroups thus leading to wide 95% CIs.

Secondary efficacy results showed that the tumour response rate of the maintenance therapy (CR + PR) was 4.2% in the pemetrexed arm and 1.1% in the placebo arm (p=.067).

Results of the first preliminary survival analysis showed a preliminary improvement of the median of 1.57 months. Survival was immature with high censoring rates (78.6% and 74.4% for the pemetrexed and placebo arms, respectively). For a second preliminary analysis of OS results, 299 events had occurred with censoring rates of 48% and 38% in the pemetrexed and placebo arms, respectively. The hazard ratio was 0.78 (95% CI: 0.61 to 0.98; log rank p= 0.034). The median OS benefit for patients receiving pemetrexed was 2.76 months.

- Uncertainty in the knowledge about the beneficial effects

There are no significant uncertainties in the knowledge of the beneficial effects.

Risks

- Unfavourable effects

Fifty six (56) deaths occurred during induction treatment of which 11 were due to study drug-related AEs. Among the 15 death due to unrelated AEs, 4 were secondary to pulmonary embolism. Comparison of data from the PARAMOUNT and JMDB studies showed a higher toxicity during JMDB. Increased toxicity could be explained by a higher exposure to pemetrexed-cisplatin (up to 6 cycles) in comparison to PARAMOUNT induction treatment (4 cycles). However, no new safety signal emerged from the comparison of the PARAMOUNT induction treatment and JMDB. Overall, the safety results observed in the PARAMOUNT study are consistent with the known safety profile of pemetrexed.

During maintenance treatment, there was no difference between placebo and pemetrexed arms in term of deaths. As expected more patients in the pemetrexed arm had dose delays due to adverse events (20.1%) in comparison to the placebo arm (14.4%). The most common reasons for dose delays in active arm were AEs related to hematotoxicity (anaemia, neutropenia, leukopenia, haemoglobin decreased). Similarly dose reductions were more frequent in pemetrexed arm (3.1%) in comparison to the placebo arm (0.6%). All the dose reductions were due to AEs.

During maintenance treatment, frequencies of SAEs and related SAEs were higher in the pemetrexed arm. However, due to the small number of SAEs, the difference between both arms was non-significant. Overall, 14 patients (3.9%) in the pemetrexed arm and 3 (1.7%) in the placebo arm, discontinued treatment due to SAEs.

- Uncertainty in the knowledge about the unfavourable effects

Pulmonary embolism is a newly identified Adverse Drug Reaction (ADR) for pemetrexed. As such, it was included in section 4.8 of the SmPC and it will be included in the next version of the RMP which the MAH proposes to submit in early 2012.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

The gain in median PFS of 1.38 months was highly statistically significant. Based on preliminary analyses, a statistically significant difference in OS has not been shown, but the preliminary difference in median OS of 2.76 months suggests that at least a detrimental effect is unlikely.

- Benefit-risk balance

The benefit-risk balance of pemetrexed as maintenance treatment after a first line platinum-pemetrexed combination is considered as positive, as the demonstrated statistically significant gain in PFS outweighs the added toxicity of pemetrexed given as maintenance treatment after induction chemotherapy with a platinum-pemetrexed combination.

Discussion on the benefit-risk balance

The PARAMOUNT study added a new piece of information on the use of pemetrexed as maintenance treatment of NSCLC other than predominantly squamous cell histology after first line induction treatment with platinum chemotherapy that included pemetrexed. Two questions resulting from the pemetrexed maintenance treatment had been: 1) whether the OS benefit observed in trial JMEN was only due to the delayed administration of otherwise efficacious pemetrexed and 2) whether pemetrexed maintenance is beneficial (even) after pemetrexed induction. PARAMOUNT showed that patients derive additional benefit from continuing pemetrexed as maintenance treatment after induction chemotherapy which includes pemetrexed.

Based on PARAMOUNT and earlier studies in both maintenance (JMEN) and first-line (JMDB) treatment, there is little uncertainty in the knowledge of favourable and unfavourable effects in the use of pemetrexed as maintenance treatment after a first line platinum-pemetrexed combination to change the benefit-risk balance.

4. Conclusion

On 22 September 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

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